Amendments to the Claims

This listing of claims will replace all prior versions and listings of claims in the application:

- 1. (presently amended) A pharmaceutical composition comprising:
- (a) one or morean anticholinergies of formula 1

wherein X- denotes is an anion with a single negative charge; and

(b) one or morean EGFR kinase inhibitors (2), wherein the PDE-IVEGFR kinase inhibitor is optionally in the form of an enantiomer, a mixture of enantiomers, a racemate, a solvate, or a hydrate thereof,

optionally together with one or more pharmaceutically acceptable excipients.

- 2. (presently amended) A pharmaceutical composition according to claim 1, wherein X^{-} denotes is an anion selected from chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate, and p-toluenesulphonate.
- 3. (cancelled)
- 4. (presently amended) A pharmaceutical composition according to claim 1, wherein in the compound of formula $\underline{1} X^-$ is a negatively charged anion selected from chloride, bromide, 4-toluenesulphonate, and methanesulphonate.
- 5. (presently amended) A pharmaceutical composition according to claim 1, wherein in the compound of formula 1 X denotes is bromide.

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- 6. (presently amended) A pharmaceutical composition according to claim 1, wherein the EGFR kinase inhibitor 2 is selected from:
- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-(2-{4-[(S)-(2-oxo-tetrahydrofuran-5-yl)carbonyl]-piperazin-1-yl}-ethoxy)-6-[(vinylcarbonyl)amino]-quinazoline-;
- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-6-[(vinylcarbonyl)amino]-quinazoline;
- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((*R*)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline;
- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((S)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline:
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[2-(ethoxycarbonyl)-ethyl]-N-[(ethoxycarbonyl)methyl]amino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline;
- $4-[(R)-(1-phenyl-ethyl)amino]-6-\{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino\}-7-cyclopropylmethoxy-quinazoline;:$
- $4-[(R)-(1-phenyl-ethyl)amino]-6-\{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino\}-7-cyclopentyloxy-quinazoline,$

- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((*R*)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline_{$\frac{1}{2}$}
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline;
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline;
- 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline;
- 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline;
- 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline;
- 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline;

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4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-
7-((S)-tetrahydrofuran-3-yloxy)-quinazoline;
4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-
buten-1-yl}amino)-7-cyclopentyloxy-quinazoline;
4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-
1-yl]amino}-7-cyclopentyloxy-quinazoline;;
4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-
7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline
4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-
7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline
4-[(3-chloro-4-fluorophenyl)amino]-6-[3-(morpholin-4-yl)-propyloxy]-7-methoxy-
quinazoline;
4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline
4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinyl-
carbonyl)amino]-quinazoline;
4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine;
3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-
yl]amino}-7-ethoxy-quinoline,
4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-(5-{[(2-methansulfonyl-
ethyl)amino|methyl}-furan-2-yl)quinazoline;
Cetuximab,
Trastuzumab;
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-ABX-EGF; and

Mab ICR-62,

optionally in the form of a physiologically acceptable acid addition salt thereof.

- 7. (presently amended) A pharmaceutical composition according to claim 1, wherein the EGFR kinase inhibitor 2 is selected from:
- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-(2-{4-[(S)-(2-oxo-tetrahydrofuran-5-yl)carbonyl]-piperazin-1-yl}-ethoxy)-6-[(vinylcarbonyl)amino]-quinazoline;
- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-6-[(vinylcarbonyl)amino]-quinazoline:
- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline;
- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((S)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline;
- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-(2,2-dimethyl-6-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazolineix
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline;

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4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[2-(ethoxycarbonyl)-ethyl]-N-
[(ethoxycarbonyl)methyl]amino]-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-
quinazoline;
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4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline-;
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4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline;
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4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline;
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4-[(3-chloro-4-fluoro-phenyl)amino]-6-({4-[bis-(2-methoxyethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline;

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline;

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline;

4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline

4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline;

4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((S)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline;

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4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline;
4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-
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yl}amino)-7-cyclopropylmethoxy-quinazoline;

4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline;

4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline;

4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline;

4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(4-dimethylamino-cyclohexyl)amino]-pyrimido[5,4-d]pyrimidine; and

4-[(3-chloro-4-fluorophenyl)amino]-6-[3-(morpholin-4-yl)-propyloxy]-7-methoxy-quinazoline,

optionally in the form of a physiologically acceptable acid addition salt thereof.

- 8. (presently amended) A pharmaceutical composition according to claim 1, wherein the EGFR kinase inhibitor is selected from:
- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline;
- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((S)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline;
- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-(2-{4-[(S)-(2-oxo-tetrahydrofuran-5-yl)carbonyl]-piperazin-1-yl}-ethoxy)-6-[(vinylcarbonyl)amino]-quinazoline;
- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-6-[(vinylcarbonyl)amino]-quinazoline;
- 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[2-(ethoxycarbonyl)-ethyl]-N-[(ethoxycarbonyl)methyl]amino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline;
- 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline; and
- 4-[(3-chloro-4-fluorophenyl)amino]-6-[3-(morpholin-4-yl)-propyloxy]-7-methoxy-quinazoline,

optionally in the form of a physiologically acceptable acid addition salt thereof.

- 9. (presently amended) A pharmaceutical composition according to claim 1, wherein the weight ratios of the anticholinergic to the EGFR kinase inhibitor are in the range from 1:300 to 60:1.
- 10. (presently amended) A pharmaceutical composition according to claim 1, wherein the weight ratios of the anticholinergic1 to 2the EGFR kinase inhibitor are in the range from 1:200 to 30:1.
- 11. (presently amended) A pharmaceutical composition according to claim 1, wherein a single dose for administration corresponds to a dose of the active substance combination of the anticholinergic 1 and 2 the EGFR kinase inhibitor of 1000 µg to 100,000 µg.
- 12. (presently amended) A pharmaceutical composition according to claim 1, wherein a single dose for administration corresponds to a dose of the active substance combination of the anticholinergic-1 and the EGFR kinase inhibitor of 1500 µg to 50,000 µg.
- 13. (presently amended) A pharmaceutical composition according to claim 1, wherein it the pharmaceutical composition is in the form of a formulation suitable for inhalation.
- 14. (presently amended) A pharmaceutical composition according to claim 13, wherein itthe pharmaceutical composition is a formulation selected from inhalable powders, propellant-containing inhalable aerosols, or and propellant-free inhalable solutions or suspensions.
- 15. (presently amended) A pharmaceutical composition according to claim 14, wherein the pharmaceutical compositionit is an inhalable powder which comprises comprising the anticholinergic and the EGFR kinase inhibitor in admixture with a suitable physiologically acceptable excipient selected from monosaccharides, disaccharides, oligo- and polysaccharides, polyalcohols, salts, or mixtures of these excipients with one another.
- 16. (presently amended) An inhalable powder according to claim 15, wherein the excipient has a maximum average particle size of up to 250 µm

- 17. (presently amended) An inhalable powder according to claim 15, wherein the excipient has a maximum average particle size of between 10 μm and 150 μm.
- 18. (presently amended) A capsule containing an inhalable powder according to claim 15.
- 19. (presently amended) A pharmaceutical composition according to claim 14, wherein itthe pharmaceutical composition is an inhalable powder consisting of which contains only substances the anticholinergic 1 and the EGFR kinase inhibitor 2 as its ingredients.
- 20. (presently amended) A pharmaceutical composition according to claim 14, wherein the pharmaceutical composition it is a propellant-containing inhalable aerosol which contains containing the anticholinergic—1 and 2the EGFR kinase inhibitor in dissolved or dispersed form.
- 21. (presently amended) A propellant-containing inhalable aerosol according to claim 20, further comprising containing a propellant gas selected from a hydrocarbon or halohydrocarbon.
- 22. (presently amended) A propellant-containing inhalable aerosol according to claim 20, containing further comprising a propellant gas selected from n-propane, n-butane, isobutene, or chlorinated and/or fluorinated derivatives of methane, ethane, propane, butane, cyclopropane, or cyclobutane.
- 23. (original) A propellant-containing inhalable aerosol according to claim 21, wherein the propellant gas is TG11, TG12, TG134a, TG227, or a mixture thereof.
- 24. (original) A propellant-containing inhalable aerosol according to claim 21, wherein the propellant gas is TG134a, TG227, or a mixture thereof.
- 25. (presently amended) A propellant-containing inhalable aerosol according to claim 20, wherein it optionally contains further comprising one or more other ingredients selected from cosolvents, stabilisers, surfactants, antioxidants, lubricants, and means for adjusting the pH.

- 26. (presently amended) A propellant-containing inhalable aerosol according to claim 20, wherein it the propellant-containing inhalable aerosol contains up to 5 wt.-% of active substance the anticholinergic and/or the EGFR kinase inhibitor active substances.
- 27. (presently amended) A pharmaceutical composition according to claim 14, wherein itthe pharmaceutical composition is a propellant-free inhalable solution or suspension which contains a solvent selected from water, ethanol, or a mixture of water and ethanol.
- 28. (presently amended) An inhalable solution or suspension according to claim 27, wherein the pH is $2 \underline{to} 7$.
- 29. (presently amended) An inhalable solution or suspension according to claim 27, wherein the pH is $2-\underline{to}$ 5.
- 30. (presently amended) An inhalable solution or suspension according to claim 28, wherein the pH is adjusted by means of an acid selected from hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid, and propionic acid, or mixtures thereof.
- 31. (presently amended) An inhalable solution or suspension according to claim 27, wherein <a href="https://doi.org/10.1001/journal.org/10.1001/jo
- 32. (presently amended) An inhalable solution or suspension according to claim 31, <u>further comprisingeontaining</u> a co-solvent selected from ingredients which contain hydroxyl groups or other polar groups.
- 33. (presently amended) An inhalable solution or suspension according to claim 31, containing further comprising a co-solvent selected from isopropyl alcohol, propyleneglycol, polyethyleneglycol, polypropylene_glycol, glycol_ether, glycerol, polyoxyethylene alcohols, and polyoxyethylene fatty acid esters.
- 34. (presently amended) An inhalable solution or suspension according to claim 31, eontaining further comprising an excipient selected from surfactants, stabilisers, complexing

agents, antioxidants and/or preservatives, flavorings, pharmacologically acceptable salts, and/or vitamins.

- 35. (presently amended) An inhalable solution or suspension according to claim 34, eontaining further comprising a complexing agent selected from editic acid or a salt of editic acid.
- 36. (presently amended) An inhalable solution or suspension according to claim 35, <u>further comprising</u> containing sodium edentate.
- 37. (presently amended) An inhalable solution or suspension according to claim 34, <u>further comprising containing</u> an antioxidant selected from ascorbic acid, vitamin A, vitamin E, and tocopherols.
- 38. (presently amended) An inhalable solution or suspension according to claim 34, eontaining further comprising a preservative selected from cetyl pyridinium chloride, benzalkonium chloride, benzoic acid, and benzoates.
- 39. (presently amended) An inhalable solution or suspension according to claim 31, consisting of containing, in addition to the substances anticholinergic. 1 and 2 the EGFR kinase inhibitor, and the solvent, only benzalkonium chloride, and sodium edetate.
- 40. (presently amended) An inhalable solution or suspension according to claim 31, consisting of containing, in addition to the anticholinergic substances 1 and 2the EGFR kinase inhibitor, and the solvent, only and benzalkonium chloride.
- 41. (presently amended) An inhalable solution or suspension according to claim 27, wherein the inhalable solution or suspensionit is a concentrate or a sterile ready-to-use inhalable solution or suspension.
- 42. (original) An inhaler containing a capsule according to claim 18.
- 43. (original) An inhaler containing an inhalable solution according to claim 27.

- 44. (original) A nebuliser containing an inhalable solution according to claim 41.
- 45. (original) A method of treating an inflammatory or obstructive disease of the respiratory tract comprising administering to a patient in need of such treatment a therapeutically effective amount of a pharmaceutical composition according to claim 1.